Amendments to the Specification

Please replace the paragraph beginning on page 1, line 30 and ending on page 2, line 14 with the following amended paragraph:

Scientists have explored various administration routes other than ~~the~~ injection for proteins and peptides. These routes include oral, intranasal, rectal, and vaginal cavities for the effective delivery of large molecules. Out of the above four mentioned routes, oral and nasal cavities have been of greatest interest to scientists. Both the oral and nasal membranes offer advantages over other routes of administration. For example, drugs administered through these membranes have a rapid onset of action, provide therapeutic plasma levels, avoid first pass effect of hepatic metabolism, and avoid exposure of the drug to the hostile GI environment. Additional advantages include easy access to the membrane sites so that the drug can be applied, localized and removed easily. Further, there is a good potential for prolonged delivery of large molecules through these membranes.

Please replace the paragraph at page 2, lines 15 through 25 with the following amended paragraph:

The oral routes have received far more attention than ~~has~~ have the other routes. The sublingual mucosa includes the membrane of ventral surface of the tongue and the floor of the mouth whereas the buccal mucosa constitutes the lining of the cheek. The sublingual mucosa is relatively permeable thus giving rapid absorption and acceptable bioavailability of many drugs. Further, the sublingual mucosa is convenient, acceptable and easily accessible. This route has been investigated clinically for the delivery of a substantial number of drugs.

Please replace the paragraph beginning at page 2, line 16 and ending on page 3, line 5 with the following amended paragraph:

The ability of molecules to permeate through the oral mucosa appears to be related to molecular size, lipid solubility and peptide protein ionization. Small molecules, less than 1000 daltons, appear to cross mucosa rapidly. As molecular size increases, the permeability decreases rapidly. Lipid soluble compounds are more permeable than non-lipid soluble molecules. Maximum absorption occurs when molecules are un-ionized or neutral in electrical charges. Therefore charged molecules present the biggest challenges to absorption through the oral mucose.

Please replace the paragraph at page 3, lines 6 through 18 with the following amended paragraph:

Most proteinic drug molecules are extremely large molecules with molecular weights exceeding 6000 daltons. These large molecules have very poor lipid solubility and are practically impermeable. Substances that facilitate the absorption or transport of large molecules (>2000 daltons) across biological membranes are known as ~~the~~ enhancers., (Lee, et al., Critical Reviews in Therapeutic drug Carrier Systems, 8, 91, 1991; Lee et al., Critical Reviews in Therapeutic drug Carrier Systems, 8, 115, 1991, 1992). Enhancers may be characterized as chelators, bile salts, fatty acids, synthetic ~~hydrophilic~~hydrophilic and hydrophobic compounds, and biodegradable polymeric compounds.

Please replace the paragraph beginning at page 3, line 27 and ending on page 4, line 15 with the following amended paragraph:

Many enhancers have been tested so far and some have been found to be effective in facilitating mucosal administration of large molecule drugs. However, hardly any penetration enhancing products have reached the market place. Reasons for this include lack of a satisfactory safety profile respecting irritation, lowering of the barrier function, and impairment of the

~~mucociliary~~mucociliary clearance protective mechanism. The main factor to be considered in the use of enhancers, especially those related to bile salts and some protein solubilizing agents, is extremely bitter and unpleasant taste. This makes their use almost impossible for human consumption on a daily basis. Several approaches were utilized to improve the taste of the bile salts based delivery systems, but none one of them are commercially acceptable for human consumption to date. ~~Among the approaches~~Approaches utilized includes patches for buccal mucosa, bilayer tablets, controlled release tablets, use of protease inhibitors, buccally administered film patch devices, and various polymer matrices.

Please replace the paragraph beginning at page 4, line 16 and ending on page 5, line 7 with the following amended paragraph:

The basic problem associated with the above technologies is the use of large quantities of bile acids and their salts to promote the transport of the large molecules through membranes in the form of localized delivery systems using patches or tablets. In spite of using protease inhibitors and polymer coatings the technologies failed to deliver proteinic drugs in the required therapeutic concentrations. Further, the problem is compounded because of the localized site effect of the patch which resulted in severe tissue damage in the mouth. Most attempts were made to deliver large molecules via the oral, nasal, rectal, and vaginal routes using single bile acids or enhancing agents in combination with protease inhibitors and biodegradable polymeric materials. However, it is extremely difficult to achieve therapeutic levels of proteinic drugs using these formulations, ~~As~~as single enhancing agents fail~~fails~~ to loosen tight cellular junctions in the oral, nasal, rectal and vaginal cavities for a required period of time to allow passage of large molecules through the mucosal membranes without further degradation. This problem makes it impractical to use the above mentioned systems for a commercial purpose.

Please replace the paragraph at page 5, lines 8 through 19 with the following amended paragraph:

In order to overcome the above mentioned problem of the bitter taste, irritation and the penetration of large molecules through the sublingual, buccal and GI tract mucosal lining, a system has now been designed where a proteinic drug was encapsulated in mixed micelles made up of a combination of enhancers, e.g., yolk proteins (lecithins). This system allows the opening of the paracellular junctions (tight junctions) in the oral cavity as well as in the GI tract by GIgI mortility movement with a high degree of protease activity preserved and for protecting molecules from premature degradation in the hostile acidic and proteolytic GI environment.

Please replace the paragraph at page 5, lines 20 through 28 with the following amended paragraph:

It is believed that the mixed micelles encapsulate molecules with high degree of efficiency (>90% encapsulation). These mixed micelles are extremely small in ~~the~~ size (1nm to 10nm), and are smaller than the pores of the membranes in the oral cavity or the GI tract. It is therefore believed that the extremely small size of mixed micelles helps encapsulated molecules penetrate efficiently through the mucosal membranes of the oral cavity.

Please replace the paragraph at page 6, lines 3 through 28 with the following amended paragraph:

The amount of physiologically peptide or protein in the compositions of this invention is typically a quantity that provides an effective amount of the drug to produce the physiological activity (therapeutic plasma level) for which the peptide or protein is being administered. In consideration of the fact that the bioavailability of any active substance can never be 100%, that is to say the administered dose of the active drug is not completely absorbed, it is preferable to incorporate a slightly larger amount than the desired dosage. Where the dosage form is a spray (aerosol) or the like which is repeatedly dispensed from the same container, it is recommendably

so arranged that the unit dose will be slightly greater than the desired dose. It should be understood that dosage should vary with species of warm blooded animals such as man, domestic animals, and their body weights. ~~Although the~~ The composition of this invention is prepared as ~~the~~ microfine droplets (1 to 10 nm or less) by ~~the~~ virtue of ~~its~~ the preparation methods used and suitable combinations of enhancer compound characteristics. The utilization of atomizer or aerosol spray devices (metered dose inhalers or nebulizers) may be useful to further reduce~~a sufficient reduction of~~ the particle size for effective inhalation from the nasal or oral cavity so that the drug may be successfully absorbed or reach to the specific site.

Please replace the paragraph beginning at page 6, line 29 and ending on page 7, line 12 with the following amended paragraph:

The therapeutic composition of the present invention can be stored at room temperature or at cold temperatures. Storage of proteinic drugs is preferable at ~~the~~ cold temperatures to prevent the degradation of the drugs and to extend their shelf life. While the mixed micellar therapeutic composition of the invention is applied to the mucosal membranes, the sites of administration may be the same as those used for ~~the~~ usual mucosal therapeutic preparations. Generally, oral, transdermal and nasal are the favourite sites of ~~the~~ administration but the composition can be applied to the rectal and vaginal mucosa. According to the physiologically active peptide or protein used, the dosage form and the site of administration, a specific administration method can be selected.

Please replace the paragraph at page 7, lines 13 through 15 with the following amended paragraph:

As used herein, the term "edetate" ~~is used herein to~~ refers to pharmaceutically acceptable salts of ethylenediaminetetraacetic acid.

Please replace the paragraph beginning at page 7, line 16 and ending on page 8, line 6 with the following amended paragraph:

It ~~has also been found~~ is known that improvements in penetration and absorption of mixed micellar formulations can be achieved by mixing the mixed micellar formulation with propellants such as tetrafluoroethane, heptafluoroethane, dimethylfluoropropane, tetrafluoropropane, butane, isobutane, dimethyl ether and other non-CFC and CFC propellants. Preferably they are delivered through metered dose spray devices. Metered dose inhalers are known and are popular pulmonary drug delivery form for some drugs. The present formulation, including the propellant, is intended to improve the quality of absorption, stability and performance of many formulations. The compositions have been selected to give enhancement in the penetration through pores, and facilitate absorption of the drugs to reach therapeutic levels in the plasma. The present formulation may be absorbed buccally, by ensuring that the person does not inhale the formulation as it is sprayed. One of the other benefits of using an atomizer or inhaler is that the potential for contamination is minimized because the devices are self contained.

Please replace the paragraph at page 8, lines 7 through 30 with the following amended paragraph:

Summary of the Invention

Accordingly the present invention provides a mixed micellar pharmaceutical formulation, having a pH of between 6.0 and 7.0 comprising a proteinic pharmaceutical agent in micellar form, water, an alkali metal lauryl sulphate in a concentration of from 1 to 10 wt./wt. % of the total formulation, a pharmaceutically acceptable edetate in a concentration of from 1 to 10 wt./wt/% of the total formulation, at least one alkali metal salicylate in a concentration of from 1 to 10 wt./wt.% of the total formulation, and at least one micelle forming compound selected from the group consisting of lecithin, hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid, octylphenoxypolyethoxyethanol, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linolenic acid, borage oil, evening ~~of~~ primrose oil, trihydroxy oxo

cholanylglycine, glycerin, polyglycerin, lysine, polylysine, triolein and mixtures thereof, wherein ~~the amount of~~ each absorption enhancing compound is present in a concentration of from 1 to 10 wt./wt.% of the total formulation, and the total concentration of absorption enhancing compounds ~~are~~ is less than 50 wt./wt.% of the formulation.

Please replace the paragraph at page 9, lines 4 through 7 with the following amended paragraph:

In one embodiment, the edetate is an alkali metal edetate. Preferably the alkali metal edetate ~~is~~ be selected from the group consisting of disodium edetate, dipotassium edetate, and combinations thereof.

Please replace the paragraphs beginning at page 9, line 19 and ending on page 10, line 31 with the following amended paragraphs:

In one embodiment, one of the absorption enhancing compounds is selected from the group consisting of hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid and mixtures thereof, the concentration of such micelle forming compound being from about 1 to about 5 wt./wt%.

In another embodiment, suitable for delivery through nasal passages, the mixed micellar pharmaceutical formulation is suitably diluted to avoid irritation of the nasal passages.

Another aspect of the present invention provides a mixed micellar pharmaceutical formulation, comprising a pharmaceutical agent in micellar form, water, an alkali metal C8 to C22 alkyl sulphate in a concentration of from 1 to 10 wt./wt.% of the total formulation, a pharmaceutically acceptable edetate in a concentration of from 1 to 10 wt./wt.% of the total formulation, at least one alkali metal salicylate in a concentration of from 1 to 10 wt./wt.% of the total formulation, and at least one micelle forming compound selected from the group consisting of lecithin, hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid, octylphenoxypolyethoxyethanol, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linolenic acid, borage oil, evening ~~of~~ primrose oil, menthol, trihydroxy oxo

cholanylglycine and pharmaceutically acceptable salts thereof, glycerin, polyglycerin, lysine, polylysine, polidocanol alkyl ethers and analogues thereof, triolein and mixtures thereof, wherein ~~the amount of~~ each absorption enhancing compound is present in a concentration of from 1 to 10 wt./wt.% of the total formulation, and the total concentration of absorption enhancing compounds ~~are~~is less than 50 wt./wt.% of the formulation.

Yet another aspect of the present invention provides that the mixed micellar aerosol pharmaceutical formulation additionally comprises ~~i)~~ a phenolic compound selected from the group consisting of phenol and methyl phenol in a concentration of from 1 to 10 wt./wt.% of the total formulation, and ~~ii)~~ a propellant selected from the group consisting of C1-C2 dialkyl ether, butanes, fluorocarbon propellant, hydrogen-containing fluorocarbon propellant, chlorofluorocarbon propellant, hydrogen-containing chlorofluorocarbon propellant, and mixtures thereof.

Please replace the paragraph at page 11, lines 11 through 18 with the following amended paragraph:

In yet another embodiment, one of the micelle forming compounds is selected from the group consisting of hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid, polidocanol alkyl ethers, trihydroxy oxo cholanyl glycine, polyoxyethylene ethers and mixtures thereof, the concentration of such absorption enhancing compound being from about 1 to about 5 wt./wt. %.

Please replace the paragraph beginning at page 11, line 29 and ending on page 12, line 5 with the following amended paragraph:

For insulin-containing and some other compositions, the composition may also contain~~contains~~ at least one inorganic salt which opens channels in the gastrointestinal tract and may provide additional stimulation to release insulin. Non-limiting examples of inorganic salts are sodium, potassium, calcium and zinc salts, especially sodium chloride, potassium chloride, calcium chloride, zinc chloride and sodium bicarbonate.

Please replace the paragraph beginning at page 12, line 26 and ending on page 15, line 3 with the following amended paragraphs:

Non-limiting examples of effective protease inhibitors are bacitracin, soyabean trypsin, aprotinin and bacitracin derivatives, e.g. bacitracin methylene disalicylate. Bacitracin is the most effective of those named when used in concentrations of from 1.5 to 2 st./wt.%. Soyabean trypsin and aprotinin ~~two~~ may be used in concentrations of about 1 to 2 wt./wt.% of the formulation.

The formulation suitable for delivery through oral mucosal membranes may be in chewable form, in which case it will be necessary to add ingredients suitable for such form. Such ingredients include guar gum, powdered acacia, carrageenan~~carrageenin~~, beeswax and xanthan gum.

The pharmaceutical agent may be selected from a wide variety of macromolecular agents, depending on the disorder being treated, generally with molecular weights greater than about 1000 and especially between about 1000 and 2 000 000. Preferred pharmaceutical agents are selected from the group consisting of insulin, heparin, low molecular weight heparin, hirulog, hirugen, huridin~~huridine~~, interferons, interleukins, cytokines~~cytokins~~, mono and polyclonal antibodies, immunoglobins, chemotherapeutic agents, vaccines, glycoproteins, bacterial toxoids, hormones, calcitonins, insulin like growth factors (IGF), glucagon like peptides (GLP-1), large molecule antibiotics, protein based thrombolytic compounds, platelet inhibitors, DNA, RNA, gene therapeutics and antisense oligonucleotides, and small molecule drugs, e.g. opioids, narcotics, analgesics, NSAIDS, steroids, hypnotics, pain killers, morphine and the like.

The present invention also provides a process for making a pharmaceutical composition suitable for delivery through transdermal membranes comprising: a) preparing a proteinic pharmaceutical agent composition in micellar form in a aqueous medium which has an alkali metal salicylate in a concentration of from 1 to 10 wt./wt.% of the aqueous micellar pharmaceutical agent composition, an alkali metal lauryl sulphate in a concentration of from 1 to 10 wt./wt.% of the aqueous micellar pharmaceutical agent composition and a pharmaceutically acceptable edetate in a concentration of from 1 to 10 wt./wt.% of the aqueous micellar

pharmaceutical agent composition; b) slowly adding the micellar proteinic pharmaceutical agent composition to at least one of the absorption enhancing compounds selected from the group consisting of lecithin, hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid, octylphenoxypolyethoxyethanol, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linolenic acid, borage oil, evening ~~of~~ primrose oil, trihydroxy oxo cholanylglycine, glycerin, polyglycerin, lysine, polylysine, triolein and mixtures thereof, while mixing vigorously, to form a mixed micellar composition; wherein ~~the amount of the~~ each absorption enhancing compounds ~~are each~~ is present in a concentration of from 1 to 10 wt./wt.% of the total formulation, and the total concentration of alkali metal salicylate, alkali metal lauryl sulphate, edetate and absorption enhancing compounds is less than 50 wt./wt.% of the formulation.

In one embodiment, the process provides an additional step of adding, while continuing vigorous mixing, at least one absorption enhancing compound different from that added in step b), selected from the group consisting of lecithin, hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid, octylphenoxypolyethoxyethanol, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linolenic acid, borage oil, evening ~~of~~ primrose oil, trihydroxy oxo cholanylglycine, glycerine, polyglycerin, lysine, polylysine, triolein and mixtures thereof.

Please replace the paragraph at page 15, lines 11 through 15 with the following amended paragraph:

In yet another embodiment, the formulation has a combinations selected from the group consisting of i) sodium hyaluronate and unsaturated phospholipid, ii) Phospholipon-H and glycolic acid, and iii) sodium hyaluronate and lecithin.

Please replace the paragraphs beginning at page 15, line 16 and ending on page 17, line 4 with the following amended paragraphs:

The present invention also provides a process for making a pharmaceutical composition suitable for delivery by means of an aerosol comprising:

a) preparing a pharmaceutical agent composition in micellar form in an aqueous medium which has an alkali metal C8 to C22 alkyl sulfate in a concentration of from 10 to 10 wt./wt. % of the aqueous micellar pharmaceutical agent composition, and pharmaceutically acceptable edetate in a concentration of from 1 to 10 wt./wt. % of the aqueous micellar pharmaceutical agent composition, at least one alkali metal salicylate in a concentration of from 1 to 10 wt./wt. % of the aqueous micellar pharmaceutical agent composition;

b) slowly adding the micellar proteinic pharmaceutical agent composition to at least one of the absorption enhancing compounds selected from the group consisting of lecithin, hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid, octylphenoxypolyethoxyethanol, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linolenic acid, borage oil, evening ~~of~~ primrose oil, menthol, trihydroxy oxo cholanylglycine and pharmaceutically acceptable salts thereof, glycerin, polyglycerin, lysine, polylysine, polidocanol alkyl ethers and analogues thereof, triolein and mixtures thereof, while mixing vigorously, to form a mixed micellar composition; and optionally

c) an additional step of adding, while continuing vigorous mixing, at least one micelle forming compound different from that added in step b), selected from the group consisting of lecithin, hyaluronic acid, pharmaceutically acceptabel salts of hyaluronic acid, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linoleic acid, linolenic acid, monoolein, borage oil, evening ~~of~~ primrose oil, glycerin, polyglycerin, lysine, polylysine, triolein, polyoxyethylene ethers and analogues thereof, polidocanol alkyl ethers and analogues thereof, and mixtures thereof;

d) mixing the mixed micellar composition resulting from steps a) to c) with a phenolic compound selected from the group consisting of phenol, m-cresol and mixtures thereof; and subsequently

e) placing the formulation into an aerosol dispenser and charging the dispenser with a propellant;

wherein each of the absorption enhancing compounds ~~are~~is present in a concentration of from 1 to 10 wt./wt. % of the total formulation, and the total concentration of alkali metal salicylate, alkali metal C8 to C2 alkyl sulphate, edetate and absorption enhancing compounds is less than 50 wt./wt. % of the formulation.

Please replace the paragraph beginning at page 17, line 23 and ending on page 18, line 8 with the following amended paragraph:

For example, hormones which may be administered with the present invention include thyroids, androgens, estrogens, prostaglandins, somatotropins, gonadotropins, erythropoetin, interferons, interleukins, steroids and cytokines~~cytokins~~. Vaccines which may be administered with the present invention include bacterial and viral vaccines such as vaccines for hepatitis, influenza, tuberculosis, canary pox, chicken pox, measles, mumps, rubella, pneumonia, BCG, HIV and AIDS. Bacterial toxoids which may be administered using the present invention include diphtheria, tetanus, pseudomonas~~pseudonomas~~ and mycobacterium~~mycobactrium~~ tuberculosis. Examples of specific cardiovascular or thrombolytic~~thromobolytic~~ agents include heparin, hirugen, hirulos and hirudin. Large molecules usefully administered with the present invention include monoclonal antibodies, polyclonal antibodies and immunoglobins.

Please replace the paragraphs beginning on page 19, line 19 and ending on page 20, line 17 with the following amendment paragraphs:

In the case of insulin, which is intended for administration through nasal or oral cavities, the first micellar solution may be made by adding a buffer solution to powdered insulin, and then stirring until the powder is dissolved and a clear solution is obtained. A typical buffer solution is an aqueous solution of sodium salicylate and sodium lauryl sulphate and disodium edetate. Typical concentrations of sodium salicylate and sodium lauryl sulphate in the aqueous solution are about 3 to 20 wt./wt. % of each compound in the solution. Typically, insulin is present in the micellar solution in an amount which will give a concentration of about 2 to 4 wt./wt. % of the final formulation. Typically the concentration may be about 10 wt./wt. % of the first micellar composition.

The micellar solution is then added slowly to the first absorption enhancing compound, e.g. lecithin while mixing vigorously, e.g. sonicating, to form a mixed micellar~~micelle liposomal~~ solution. At least one other absorption enhancing compounds selected from the group consisting of lecithin, hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid,

octylphenoxypolyethoxyethanol, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linolenic acid, borage oil, evening ~~of~~ primrose oil, trihydroxy oxo cholanylglycine, glycerin, polyglycerin, lysine, polylysine, triolein is then added. The mixing may be done with a high speed mixer or sonicator to ensure uniform micelle particle size distribution within the formulation.

Please replace the paragraph beginning on page 20, line 29 and ending on page 21, line 1 with the following amendment paragraph:

Other ingredients may be added to the mixed micellar solution. For example, flavouring agents, antioxidants, salts, protease inhibitors or other pharmaceutically acceptable compounds may be added.

Please replace the paragraphs beginning on page 21, line 8 and ending on page 21, line 31 with the following amendment paragraphs:

The specific concentrations of the essential ingredients can be determined by relatively straightforward experimentation. For absorption through the nasal and oral cavities, it is often desirable to increase, e.g. double or triple, the dosage which is normally required through injection or~~of~~ administration through the gastrointestinal tract.

As will be understood, the amount of each component of the formulation will vary depending on the pharmaceutical agent and the site of application. Preferred formulations for oral or nasal application have the following combinations: i) sodium lauryl sulphate, sodium salicylate, disodium edetate, Phospholipon-H and sodium hyaluronate; ii) sodium lauryl sulphate, sodium salicylate, disodium edetate, lecithin and sodium hyaluronate; iii) sodium lauryl sulphate, sodium salicylate, disodium edetate, sodium hyaluronate and evening ~~of~~ primrose oil; iv) sodium lauryl suphate, sodium salicylate, disodium edetate, Phospholipon-H and bacitracin; v) sodium lauryl sulphate, sodium salicylate, disodium edetate, Phospholipon-H, sodium hyaluronate and bacitracin; and vi) sodium lauryl sulphate, sodium salicylate, disodium edetate, sodium hyaluronate, oleic acid and gamma linoleic acid.

Please replace the paragraphs beginning at page 22, line 11 and ending on page 23, line 4 with the following amended paragraphs:

As indicated hereinbefore, generally, oral and nasal are the favourite routes~~sites~~ of ~~the~~ administration but the composition can be applied to the rectal and vaginal mucosa. According to the physiologically active peptide or protein used, the dosage form and the site of administration, a specific administration method can be selected.

The composition of this invention is generally prepared as microfine mixed micellar particles (1 to 10 nm or less) by ~~the~~ virtue of the~~its~~ preparation methods used and suitable combinations of absorption enhancer characteristics.

For oral and nasal application, sprays are preferable, but ~~also~~ drops, chewable tablets, chewable gum and other suitable forms may be use. Utilization of atomizer or aerosol spray devices (metered dose inhalers or nebulizers) can be used to further reduce the particle size for effective inhalation from the nasal or oral cavity so the drug may successfully reach to the specific site and be absorbed. It is also possible to utilize a drug delivery system such that an enteric coating is applied to the gelatin capsule to cause the micelles to be released only in the duodenum or in the proximity of the large intestine and not in the stomach.

Please replace the paragraph on page 23, lines 23 through 30 with the following amended paragraph:

On the first day, the volunteers received 10 units of insulin by injection (regular fast acting insulin, available from Eli Lilly). On the second day, the volunteers received 100 units (1 mL volume per drop, approximately 20 drops) of the above-prepared oral insulin (10 times the injection dose). In both tests, blood glucose levels were monitored every 15 minutes by Bayer's Glucometer Elite.

Please replace the paragraph beginning on page 24, line 28 and ending on page 25, line 3 with the following amended paragraph:

These tests indicated that compared to the injection method, oral insulin gives a faster onset of action and lowers blood glucose levels without creating a hypoglycaemic condition. Due to the hepatic glucose production, there was a rebound effect. This is believed to be due to the incomplete absorption of insulin.

Please replace the paragraph on page 31, lines 5 through 13 with the following amended paragraph:

Separately, 100 mg of powdered Phosphatidylcholine-H~~Phosphatidylcholin-H~~ was added to a glass beaker and to this powder was added 10 mL 50% ethanol. The powder was dissolved completely. To this solution 16 mg (400 units) of micellar insulin solution dissolved in 3 mL of the buffer solution to (give 30 units/mL insulin solution) was added slowly with vigorous mixing, to form a mixed micellar solution. To this was added 0.6 mL of sodium hyaluronate and 0.2 ml of 2% menthol solution containing 3% sorbitol.

Please replace the paragraph on page 41, lines 9 through 12 with the following amended paragraph:

To this micellar solution were added 0.2 g bacitracin and 0.5 g evening ~~of~~ primrose oil and the solution was mixed vigorously to form a mixed micellar insulin solution (about 20 units/mL).

Please replace the paragraph on page 43, lines 4 through 21 with the following amended paragraph:

To this flask was added micellar insulin solution which had been prepared from an aqueous solution of insulin, sodium lauryl sulphate, sodium salicylate and disodium edetate. The

flask was shaken with the help of shaker plate. Shaking was continued for at least 30 minutes and then the solution was sonicated with a high frequency sonicating probe for another 60 minutes in order to form small uniform mixed micelles. The mixed micelles so obtained were analyzed by Malvern Zeta (trade mark) particle size distribution measurement equipment equipped with the laser light scattering device. The mixed micelles particle size distribution obtained by this method was between 2 and 9 nm. To this solution was added 1 mL of 2% menthol solution and 50 mg sodium hyaluronate. The semi-clear, translucent, light blue colour solution (final volume 10 mL) was stored in a clean glass bottle and refrigerated. The solution has a pH of 6.5.